Reviewer's report

**Title:** Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death

**Version:** 1  **Date:** 15 March 2011

**Reviewer:** David Church

**Reviewer's report:**

The authors provide a retrospective analysis of patients treated in their institution, which suggests favourable prognosis in patients with brain metastases from HER2 overexpressing metastatic breast cancer treated with trastuzumab. This is consistent with other retrospective studies previously published.

**Major essential revisions:**

1. The paper purports to report the prognostic effect of trastuzumab on the survival of patients with BM from MBC. However the group described as 'trastuzumab treated' actually refers to trastuzumab treatment during any stage of the disease course. Thus unless previous trastuzumab treatment is suggested to modify the survival of patients who develop brain metastases after discontinuation of therapy this analysis is problematic. Alternative analysis should be either:

   A. survival from time of BM: HER2 neg vs HER2 pos then subgroup analysis of HER2 pos treated with trastuzumab after BM vs not treated with trastuzumab after BM

   B. survival from diagnosis of metastatic disease: HER2 neg vs. HER2 pos trastuzumab treated vs. HER2 pos trastuzumab non-treated

   Patients with HER2 pos disease not treated with trastuzumab were poorer PS and older- suggesting that the worse survival in this group is due to selection bias. Additionally these patients may have been treated pre-2001. Though a difference in survival was noted between patients with HER2 pos disease treated with trastuzumab after BM compared to those who stopped at diagnosis of BM this is not significant. Either the analysis should be revised including survival curves, or the conclusions of the paper should be modified, and the bias in the study explicitly stated. In particular the abstract wording implies trastuzumab therapy after diagnosis of BM and should be reworded.

2. The manuscript should state the status of extracranial disease in patients diagnosed with BM in each group- not just the trastuzumab-treated cohort. Was it responding/stable/progressive?

3. No information on treatment of patients after diagnosis of BM other than WBRT is mentioned. Were other therapies- surgery, stereotactic radiosurgery, hormone therapy, chemotherapy used? In what proportion of patients? In case of systemic therapy, did continued control of extracranial disease correlate with survival?
Were there any documented intracranial responded to systemic therapy (presumably not)? This requires inclusion in table form.

Minor essential revisions:
1. p11 ‘in agreement with two previous reports...’ should be three previous reports including Church DN et al 2008
2. Please use consistent nomenclature throughout manuscript: HER2, italics for gene, non-italics for protein; 95% confidence interval (CI); P or p for significance;
3. p6 selectionned? Please reword.
4. p7 please note numbers in each group at first mention of groups
5. p7 should read ‘more likely to have received’
6. ‘brain failure’ should be changed to ‘progression within the brain’ or ‘CNS progression’
11. BMBC ?
12. multiple ‘BM patients’ should be changed to ‘patients with BM’
13. Tables- please make consistent and put P values on same lines. Please standardise no. of decimal places for P values. Percentages should be given to one decimal place.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have previously received travel expenses and honoraria from Roche.
I have no other competing interests